REMARKS

This amendment is responsive to the Office Action mailed February 17, 2006. Claims 1-31, 36-45 and 69-71 are under examination in the present action. Claims 32-35, 46-68, 72 and 73 have been withdrawn.

A certified copy of the UK priority application, GB 0224909.2, filed October 25, 2002, is included herewith. Applicants submit that the conditions for valid priority claim under 35 U.S.C. §119(a-d) have thus been fulfilled and that the effective filing date is the priority date of the application, *i.e.*, October 25, 2002.

Response to issues presented under 35 U.S.C. §112, second paragraph

Claim 41 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner objects to the recitation "wherein the composition comprises the additional features described in claim 27."

Applicants have amended Claim 41 to now expressly recite the additional features previously incorporated from Claim 27. Claim 41 now reads:

> "41. The dry composition as claimed in claim 36 wherein the composition further comprises a sweetener selected from the group consisting of aspartame, acesulfame K, saccharine and citric acid."

Support for the amendment is apparent from original Claim 41 and Claim 27. No new matter is added.

Response to issues presented under 35 U.S.C. §103

Claims 1-31, 36-45, and 69-71 are rejected under 35 U.S.C. §103(a) as unpatentable over Borody, international publication WO 89/05659 (hereinafter "Borody") in further view of Fordtran, international publication WO 87/00754 (hereinafter "Fordtran"), US Patent No. 5,458,890 issued to Williford et al., Stedman's Medical Dictionary (22nd Edition, 1972, page 737), and the Merck Index (Monograph 8723, 1996). Specifically, the Examiner notes that Borody teaches a colon evacuant for cleansing the gastrointestinal tract which shares ingredients with that of the colon cleansing compositions of the present claims. The Examiner acknowledges differences between the Borody reference and the presently claimed colon cleansing compositions, stating that Borody, *inter alia*, fails to teach:

(i) the particularly claimed dosage amounts, ratios and osmolarity of the active composition; and

(ii) the use of magnesium sulfate, sodium ascorbate or a mixture of ascorbic acid and salts thereof as an active component of the composition.

The Examiner then concludes:

> "However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." (Office Action, page 9)

Applicants traverse. Applicants submit that the Examiner has not made a *prima facie* case of obviousness. MPEP §2143.03 states that "[t]o establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art." (emphasis added) Obviousness cannot be established using Applicants' own disclosure as a guide to merely selecting and reconstructing the claimed invention from elements scattered in the prior art:

> "When the references are in the same field as that of the applicant's invention, knowledge thereof is presumed. However, the test of whether it would have been obvious to select specific teachings and combine them as did the applicant must still be met by *identification of some suggestion, teaching, or motivation in the prior art, arising from what the prior art would have taught a person of ordinary skill in the field of the invention.*" *In re Dance*, 160 F.3d 1339, 1348, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added).

Evidence of a suggestion or motivation to combine references may be found in the references themselves or in the knowledge of one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed.Cir. 1988); *In re Jones*, 958 F.2d 347, 351, 21 USPQ2d 1941, 1943 (Fed.Cir. 1992). The motivation to combine may derive from many sources, however, the range of possible sources that may serve as evidence for a motivation to combine references "does not diminish the requirement for actual evidence. That is, the showing [of a motivation to combine] must be clear and particular." *In re Dembiczak*, 50 USPQ2d 1614, 1617, 1999 WL 246572 (Fed.Cir. 1999).

Applicants submit that there is no motivation to apply the references as suggested by the Examiner to arrive at Applicants' invention as set forth in the claims. As Applicants will show,

particularly with respect to osmolarity, the references themselves actually teach away from the present invention, and therefore the differences between the cited compositions and the presently claimed colon cleansing solutions, would not have been obvious to a person of ordinary skill in the art at the time the application was filed. In fact, as discussed below, Applicants departed from the mainstream theories and teachings in the art to arrive at their invention.

State of the art prior to Applicants' invention

Applicants submit herewith pursuant to 37 C.F.R. §1.132 the declaration of Dr. Thomas Borody, an expert in the field of gastroenterology and inventor of the subject matter of the cited international application WO 89/05659. As discussed in Applicants' specification and further emphasized in the declaration of Dr. Borody, bowel lavage solutions prior to Applicants' invention can be grouped into two categories:

1) large volume, *isosmotic* orthostatic lavage solutions typified by PEG lavage solutions; and
2) *super-hyperosmotic* solutions typified by sodium phosphate solutions.

With regard to the large volume isosmotic solutions typified by PEG lavage solutions, as pointed out by Dr. Borody in his declaration, persons skilled in the art believed effective colon cleansing solutions needed to be isosmotic, *i.e.*, to have the same total osmolarity as the blood to keep water absorption and water secretion to a minimum.

As evidenced in the Declaration of Dr. Borody, persons skilled in the art knew that a solution that was not isosmotic was likely to be associated with absorption of water from the gut into the body (if the solution was hyposmotic) or the secretion of water from the body into the gut (if the solution was hyperosmotic). The absorption of water into the body results in less fluid being in the bowel and thus less efficient cleansing (or a need for a larger dose). Secretion of water from the body into the gut generally results in blood electrolyte levels becoming imbalanced and can lead to dehydration.

By its nature, bowel cleansing involves passage of a significant quantity of fluid through the bowel. As the gut is permeable to many solutes, there is, in principle, a risk of transfer of significant quantities of solutes into or out of the bloodstream when using any bowel cleansing formulation. In the case of PEG solutions according to the cited Davis[1], Borody, and Fordtran references, they have been developed so as to result in minimal water movement and minimal electrolyte movement into and out of the bowel.

[1] Davis et al., 1980, *Gastroenterology*, 78(5), 991-995, Exhibit B in Declaration of T. Borody

As mentioned above, the alternative bowel cleansing formulations of the prior art are super-hyperosmotic solutions (*e.g.*, sodium phosphate as sold under the name Fleets Phospho-soda® or more complex mixtures that may contain PEG, such as disclosed in Cleveland[2]). Those solutions are highly concentrated solutions of salts (for example sodium phosphate) that are taken in a relatively small volume, the recommended dosage regimen for Phospho-soda® being 45ml the day before the procedure and 45ml on the day of the procedure (90ml in total). The solutions are *extremely hyperosmotic* (osmolarities of over 2000 mOsm/L). They result in a large amount of water being drawn from the bloodstream into the bowel, and it is that water that flushes the colon.

However, because the super-hyperosmotic solutions have such a significant effect on water movement, they also have a significant effect on blood electrolyte levels. Typically, a dose of super-hyperosmotic sodium phosphate results in the loss of 2.5kg of water from the body and the disturbance of serum electrolyte levels: phosphate and sodium levels are raised and potassium and calcium levels are reduced. For these reasons, super-hyperosmotic solutions (such as sodium phosphate) are counterindicated for elderly patients and some other patient groups because of the risk of hyperphosphatemia, hypocalcemia or hypokalemia. Other mixed salt solutions, such as those described in Cleveland, have been proposed which include a small amount of PEG in order to reduce the amount of salts needed to attain the high osmolarity. *See,*Cleveland at column 6, lines 34-35 and column 4, lines 50-54. Analogously to the sodium phosphate solutions, the solution of Cleveland has a calculated osmolarity of over 2300 mOsm/kg and it results in a similar loss of water from the body as sodium phosphate.

The present invention

On the other hand, the solutions of the present invention have an osmotic pressure of from 300 to 700 mOsm/kg. They are thus moderately hyperosmotic and consequently cause only a moderate amount of water to be released from the bloodstream into the gut (for example, it is seen in Example 1, Table 4 of Applicants' specification that administration of 2 liters of formulation resulted in 2.7 liters of stool). It would be expected that this movement of water would also be accompanied by an electrolyte imbalance and signs and symptoms of dehydration. Surprisingly, however, as set out in the analysis of blood samples in Example 2 of the specification, while there were some signs of dehydration, there were no clinically significant changes in blood electrolyte levels, hematocrit levels or protedemia levels when a formulation according to the invention was used.

[2] US Patent No. 6,946,149 to Cleveland ("Cleveland") made of record herein.

From the foregoing it can be seen that the state of the art at the time of Applicants' invention contained definite guidance to the person of ordinary skill: Teachings represented by the combination of the Borody and Fordtran references guided the person of ordinary skill to maintain an isosmotic solution for a particular desired effect in the gut; whereas teachings represented by the commercial Phospho-soda® (sodium phosphate) product or the Cleveland patent guided the person of ordinary skill to use super-hyperosmotic solutions designed to elicit secretion of large amounts of water into the gut but leading to electrolyte imbalance as an undesirable side effect. The effect of these teachings of the prior art as a whole, as pointed out by Dr. Borody in the accompanying declaration, was that practitioners were taught away from preparing solutions having osmolarity in the range recited in Applicants' original claims, namely, 300-700 mOsmol/kg.

Applicants' work led to the discovery that such solutions were not only surprisingly effective at low volume, with good patient compliance, but also avoided the large secretion of water and consequent electrolytic imbalance caused by solutions having very high osmolarity. In this respect alone, Applicants submit that the compositions of the present invention are distinguished from and not suggested by compositions according to the combination of Borody in view of Fordtran, Stedman's dictionary, Merck Index, and Williford, and therefore withdrawal of the rejections based on those citations is respectfully believed to be in order. In order to be completely responsive, however, to the Office Action, Applicants would like to address points of the Examiner's rationale below.

In asserting that the acknowledged differences between Borody and the present claims would have been obvious to a person of ordinary skill in the art, the Examiner states:

> "(i) Borody discloses a preferable concentration of polyethylene glycol from 30-60 grams per liter, but does not expressly teach that the concentration of polyethylene glycol may be increased greater than 60 grams to, for example, up to 350 grams per liter. However, one of ordinary skill in the art would have been motivated to do so because polyethylene glycol has significant advantages when used in bowel cleansing agents." (Office Action, page 9)

Applicants submit that this assertion is incorrect. The person of ordinary skill in the art would not, at the time of the present invention, have been motivated to increase the concentration of polyethylene glycol to greater than 60 grams/liter in a solution of the type presented by Borody. In reaching her conclusion, the Examiner has not taken into account the teachings of the Borody disclosure, nor the state of the art in general, nor the particular advantages provided by the currently claimed compositions. As Applicants discuss below, in the field of orthostatic lavage solutions, there were, at the

time of the invention, significant reasons not to increase the concentration of polyethylene glycol in such solutions.

As pointed out by Dr. Borody in his declaration, persons skilled in the art believed safe, effective colon cleansing solutions needed to be isosmotic, *i.e.*, to have the same total osmolarity as the blood to keep water absorption and water secretion to a minimum.

Persons skilled in the art knew that a solution that was not isosmotic was likely to be associated with absorption of water from the gut into the body (if the solution is hyposmotic) or the secretion of water from the body into the gut (if the solution is hyperosmotic). The absorption of water into the body results in less fluid being in the bowel and thus less efficient cleansing (or a need for a larger dose). Secretion of water from the body into the gut generally results in blood electrolyte levels becoming imbalanced and can lead to dehydration.

Thus, even if the person of ordinary skill were motivated to increase the concentration of PEG in the Borody solutions as suggested by the Examiner, that person of ordinary skill would also have thought that it was necessary to reduce the concentration of other solutes in the solution to keep the osmolarity near that of the blood (290 mOsm/kg). This assertion is supported by the cited references themselves: Applicants ask the Examiner to note that this is exactly what Fordtran had done. He had reduced the concentration of other solutes in combination with increasing the concentration of PEG – *i.e.*, sodium sulfate was removed completely from the solution.

However, the Examiner asserts that the various concentrations of the components and resulting osmolarity of Applicants' colon cleanser were merely the result of routine optimization:

> "Thus, just as the dosage amounts and ratios that would have actually been employed would have varied widely and are not seen to be inconsistent with those that would have been determined by the skilled artisan, the resultant osmolarity of the solution would also have directly varied in view of the varying amounts of active agents and is, therefore, also not inconsistent with the optimum osmolarity of the solution that would have been determined by the skilled artisan." (Office Action, page 11.) (emphasis added)

However, as the foregoing remarks and declaration of Dr. Borody have pointed out, the Examiner's position is not correct. To do as the Examiner has suggested – to increase the concentration of PEG without reducing the other solutes – would go against the established teachings regarding PEG lavage solutions. This sort of departure is outside the capability of the hypothetical "person of ordinary skill in the art" who is following the teachings of the prior art. Those teachings had remained unchanged

in the art since 1980 (Davis), that is to say, for over two decades. Any solutions that were not isosmotic were considered to have to be super-hyperosmotic, *i.e.*, in order to secrete sufficient water into the gut to effect lavage.

Surprisingly, however, when the present inventors went against those teachings and generated a solution that included a high concentration of PEG with a moderate concentration of sodium sulfate and that was moderately hyperosmotic (300-700 mOsm/kg), the formulation they created was a solution that can be used at a *lower dose* than the earlier lavage solutions and that is *more palatable* than the earlier solutions. As shown in Example 1 of Applicants' specification (*see also* Table 4 (results)), administration of 2 liters of the formulation of the invention (Formulation C) resulted in a far larger stool weight and volume than 2 liters of prior art solutions (Formulation A or B). 2735g of stools were generated on average using the formulation of the invention (Formulation C) compared with 1465g and 1862g, respectively, for formulations A and B.

Furthermore, the reduced volume and better taste of the solution of the present invention results in improved patient compliance.

Patient Compliance

For effective bowel cleansing, it is important that the whole of a bowel lavage formulation is consumed. Generally the bowel must be cleansed well in advance of a scheduled medical procedure, and thus it is generally carried out without direct medical supervision. As noted in the specification, there are two aspects that have an impact on compliance:

- Unpleasant taste of the solutions; many of the solutions have a very salty taste
- Unmanageable volumes; typically 4 liters of PEG/electrolyte solution must be consumed and many patients find that very difficult.

Reducing the volume of lavage solution to be ingested without adversely affecting the safety profile of the lavage solution has been a goal of many researchers in the field for some time. In general, there has been little success in achieving that goal. The main problem stems from the need to retain good palatability.

Taking a solution according to the Borody reference, it might be considered that simply making the solution more concentrated might achieve the same effect with a lower administered volume. It would be expected by the person of ordinary skill in the art that a more concentrated lavage solution would have a more disagreeable taste. For example, a more concentrated GOLYTELY solution was prepared by the current inventors as described under Comparative Examples on page 51 of the application

(two sachets of Kleanprep® were dissolved in 1 liter of water rather than in 2 liters). However, it was found that while the solution was effective in clearing the bowel the taste was so unpleasant that it was an unacceptable formulation.

It is thus all the more surprising that the formulations of the present invention, which comprise a significant amount of the salty-tasting PEG, sodium sulfate and electrolytes, are unexpectedly palatable. As set out at page 57, lines 3-6, in the description of Clinical Trial 1 in the application, the formulation of the invention was preferred over the prior art PEG+Electrolyte solutions.

The person of ordinary skill prior to Applicants' invention would have been reluctant to consider more concentrated PEG solutions like those of the present invention for fear of adversely affecting the taste. The fact that the composition of the invention can be used in a lower volume without any accompanying adverse effect on the taste is a surprising and unexpected effect.

In the clinical trials reported in Applicants' specification, the composition of the invention was shown to be as effective as double the volume of a PEG + Electrolytes prior art composition (Kleanprep®, a solution essentially similar to GOLYTELY®). Reducing the volume of lavage solution to be ingested improves patient compliance. In the second clinical trial reported in the present application, the composition of the invention was shown to be as effective as the prior art super-hyperosmotic sodium phosphate solution and to have a better safety profile (fewer patients needed to be excluded and there were fewer adverse events). *See*, page 61 of the specification, last paragraph.

Electrolyte Imbalance

The solutions of the present invention have an osmotic pressure of from 300 to 700 mOsm/kg. They are thus moderately hyperosmotic and they thus cause a moderate amount of water to be released from the bloodstream into the gut (for example, it is seen in Example 1, Table 4 that administration of 2 liters of formulation resulted in 2.7 liters of stool). It would be expected that the movement of water would also be accompanied by an electrolyte imbalance and signs and symptoms of dehydration. Surprisingly, however, as set out in the analysis of blood samples in Example 2, there were no clinically significant changes in blood electrolyte levels, hematocrit levels or protedemia levels when the formulation of the invention was used.

Summary

Accordingly, on closer consideration of the prior art represented by the reference combination, it is seen that this is not a situation merely of finding an optimum amount within a disclosed range. Rather,

it is a situation requiring a person of ordinary skill to breach the strict teachings of the prior art to add further PEG to a solution according to Borody while disregarding effects on isosmolarity. As further described by Dr. Borody himself in his declaration, isosmolarity was seen as crucial to avoiding electrolyte imbalance side effects and dehydration with lavage solutions, and the person of ordinary skill would have aimed to achieve isosmolarity in any PEG-based lavage formulation. Moreover, concentrated lavage solutions were expected to be unpalatable, and the person of ordinary skill would thus have been inclined not to use highly concentrated solutions.

The benefits of the use of PEG in bowel preparation solutions that the Examiner recites on page 10 of the Office Action are already present in the Borody solution. If the person of ordinary skill in the art were to attempt to obtain additional benefit by adding more PEG, an accompanying reduction in the concentration of other solutes that contribute to the osmotic load would have been imperative so as to keep the osmolarity isosmolar. The osmolarity is thus not a simple side effect of the selection of the components as asserted by the Examiner on page 11 of the Office Action. The osmolarity is a central feature of the lavage solutions and one that those skilled in the art believed must be kept equal to that of the blood.

Thus, the changes made by the Applicants do not constitute a determination of optimum quantities by routine experimentation. Instead, the formulations of the present invention use a completely new concept that goes against earlier teachings to yield a surprising result.

Accordingly, because the Examiner's suggested combination of elements is contrary to what is taught in the cited references and was understood and practiced by those skilled in the art, Applicants submit that the composition of the claims is in no way obvious to a person of ordinary skill in the art not having the benefit of Applicants' disclosure. Reconsideration and withdrawal of the rejection of Claims 1-31, 36-45, and 69-71 under 35 U.S.C. §103(a) are therefore respectfully requested.

In one final point, the Examiner observed that the Borody reference fails to teach the simultaneous use of ascorbic acid and salts thereof. However, the Examiner then alleges that since sodium ascorbate is known from the Merck Index and since Remington's Pharmaceutical Sciences discloses certain advantages of formulating a drug as a salt, it would have been *prima facie* obvious to the ordinarily skilled person to combine ascorbic acid and an ascorbate salt in a bowel cleansing composition.

The Applicants respectfully submit that the Examiner's assertion cannot be substantiated. The person of ordinary skill in the art would not, at the time of the present invention, have been motivated to include a combination of both ascorbic acid and a salt thereof, since no advantages of that course of

action were apparent in any of the prior art.

Borody describes PEG-based lavage solutions that include ascorbic acid or a salt thereof and discloses that the addition of ascorbic acid in larger than usual doses to typical lavage solutions tends to reduce the required volume for satisfactory colon evacuation (page 2, lines 30-32, of Borody WO 89/05659).

Objects of the present invention include reducing the side effects of bowel cleansing compositions. There is no suggestion in the Borody reference that such an objective can be achieved by including ascorbic acid and a salt thereof in the formulation.

The Merck Index is simply a chemical compound reference manual, and it does not refer to the use of ascorbic acid in combination with ascorbate. Nor does it teach any advantages of this combination. As the Examiner has stated, Remington's Pharmaceutical Sciences does teach that certain advantages may be gained by formulating a drug as a salt, but it does not teach the simultaneous use of a drug and its salt.

It is therefore submitted that it would not have been obvious to a person of ordinary skill in this art, when faced with the goal of reducing the side effects of bowel cleansing compositions, to combine ascorbic acid and a salt thereof. This is further corroborated by Dr. Borody in the accompanying declaration.

Applicants have discovered that the combination of ascorbic acid and an ascorbate salt does in fact provide a surprising advantage, namely that a colon cleansing solution comprising ascorbic acid and one or more salts thereof has fewer side effects than a cleansing solution comprising ascorbic acid alone. In particular, the presence of one or more salts of ascorbic acid aids the maintenance of the plasma bicarbonate level (*see*, specification at page 40, table 15).

It is seen in table 15 that the blood bicarbonate concentration was reduced by 3.4 mmol/liter when solution D (which contained 10g of ascorbic acid) was administered. In contrast, when solutions C, E or F (which each contained 5g of ascorbic acid and 5g of sodium ascorbate) were administered, the drop in bicarbonate concentration was only 1.78 mmol/liter, 1.89 mmol/liter and 0.7 mmol/liter without any loss of efficacy or palatability. Thus, the combination of ascorbic acid and sodium ascorbate gave rise to fewer side effects than the use of ascorbic acid alone, without any loss of efficacy or palatability.

Maintaining the plasma bicarbonate level is advantageous because a lowered plasma bicarbonate level can result in serious adverse clinical consequences associated with a reduced blood pH (acidosis) and consequent reduced capacity to transport CO_2 in the bloodstream. Acidosis may lead to weakness, disorientation, coma and eventually death.

It is therefore submitted that the simultaneous use of ascorbic acid and ascorbate is an additional

non-obvious improvement over the teaching of the prior art.

For the foregoing reasons, Applicants submit that the composition of the claims is in no way obvious to a person of ordinary skill in the art not having the benefit of Applicants' disclosure. Reconsideration and allowance are therefore respectfully requested.

Respectfully submitted,

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date

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